FDA Perspective on Nanomaterial-Containing Products

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FDA Mission

- **Not only to protect, but also to advance the public health by assuring safe and effective medical products and safe foods for humans and animals.**

FDA's Critical Path Initiative

- Initiative to help reduce existing hurdles in medical product design and development.
- Initiative rooted in taking advantage of innovative science and technologies to reach commercialization of medical products.
- Nanotechnology is an element under evaluation in FDA's Critical Path Initiative.

Coordination of Policy on Nanomaterials With Other Government Agencies

- FDA is a member of the Nanoscale Science and Engineering Technology (NSET) Subcommittee of the National Science and Technology Council (NSTC) Committee on Technology.
- FDA co-chairs with NIOSH the NSET Working Group on Nanomaterials Environmental and Health Implications (NEHI) to define new test methods to assess safety of these products.
- FDA contributes to the evaluation of the toxicity of materials supported by NIEHS and NTP.

FDA Activities in Nanotechnology

- Office of Science and Health Coordination (within OC) coordinates regular discussions within Agency.
- Individual Centers have regular discussion groups within each Center.
  - Purpose of these meetings is to insure awareness of policies that may be developing within the Agency and to educate staff and policy makers on scientific progress in nanotechnology.
- FDA-NCI Clinical Proteomics Program
- Interagency Oncology Task Force, Nanotechnology subcommittee, featuring collaboration between FDA-NCI-NIST

Current FDA Definition for Nanotechnology

- **FDA calls it "nanotechnology" only if it involves all of the following:**
  - **1. Research and technology development, or products regulated by FDA, that are at the atomic, molecular or macromolecular levels, and where at least one dimension, that affects the functional behavior of the product, is in the length scale range of approximately 1-100 nanometers.**
  - **2. Creating and using structures, devices and systems that have novel properties and functions because of their small and/or intermediate size.**
  - **3. Ability to control or manipulate at the atomic scale.**

FDA-Regulated Products Expected to be Impacted by Nanotechnology

- Drugs
- Drug delivery systems
- Medical devices
- Vaccines
- Biotechnology products
- Cosmetics
- Gene and protein delivery
- Combination tissue/device

Historically

- FDA has approved many products with particulate materials in the nanosize range.
- Most drugs are expected to go through a nanosize phase during the process of absorption in the body.
- There have been no safety concerns reported in the past because of particle size.

General Concerns about Nanotechnology Products

- Examples of concerns regarding:
  - Safety
  - Quality of material/characterization
  - Environmental

Safety Concerns

- As particle size gets smaller, there may be size-specific effects on activity, such as:
  - Will nanoparticles gain access to tissues and cells that normally would be bypassed by larger particles?
  - Once nanoparticles enter tissues, how long do they remain there and how are they cleared?
  - If nanoparticles enter cells, what effects do they have on cellular and tissue functions? Might there be different effects in different cells types?

Safety Concerns (Cont'd)

- What are the differences in the ADME profile of nanoparticles versus larger particles?
- What preclinical screening tests would be useful to identify potential risks (in vitro or in vivo)?
- Can new technologies such as "omics" help identify potential toxicities and how can these methodologies complement current testing requirements?
- Can nanoparticles gain access to the systemic circulation from dermal exposure? If nanoparticles enter skin cells, is there an effect on cellular functions? This would be relevant to drugs and cosmetics.

Characterization Concerns

- What are the forms in which particles are presented to host, cells and organelles?
- What are the critical physical and chemical properties, including residual solvents, processing variables, impurities and excipients?
- What are the standard tools used for this characterization?
- What are validated assays to detect and quantify nanoparticles in tissues, medical products, foods and processing equipment?
- How do physical characteristics impact product quality and performance?
- How do we determine long and short-term stability of nanomaterials?

Environmental Concerns

- Can nanoparticles be released into the environment following human and animal use?
- What methodologies would identify the nature, and quantify the extent, of nanoparticle release in the environment?
- What might be the environmental impact on other species (animals, fish, plants, microorganisms)?

Crucial Hurdles for Nanotechnology

- **Safety assessment**
  - **Adequacy of current toxicologic screens for nanoscale materials.**
  - **Potential for novel, unanticipated reactions.**
  - **Environmental consequences of medical use.**
- **Efficacy**
  - **No experience with clinical testing.**
- **Industrialization**
  - **Understanding the physical and chemical parameters that are crucial to product performance.**
  - **Developing test methods and specifications to control product/process.**
  - **Scale-up to mass production.**
  - **Lack of reference material, standards and manufacturing standardization.**

Standard Test Methods for Biological Response Including Particles

- Guidelines for evaluating biological safety for medical devices is based on application of voluntary standards
  - ASTM F 748 (F1903 in vitro and F1904 in vivo, for particles)
  - ISO 10993, Part 1
- None of the standards are specific for nanoparticles.
- Additional standard test methods may need to be developed for nanoparticles.
- No existing standards for testing particles for drugs and biologics.

Current Preclinical Tests for Safety Evaluation

- Pharmacology
- Safety pharmacology
- Toxicology (including clinical pathology and histopathologic analysis)
- ADME
- Genotoxicity
- Developmental toxicity
- Immunotoxicity
- Carcinogenicity
- Other

Adequacy of Current Preclinical Screening System?

- Existing battery of preclinical tests is currently believed to be adequate.
- Why?
  - High dose multiples used
  - At least 2 animal species used
  - Extensive histopathology on most organs
  - Functional tests (cardiac, neurologic, respiratory, reproductive, immune system, etc/…)
  - Extended treatment periods (up to 2 years for carcinogenicity studies)

FDA Research in Nanotechnology

- Examples of research in
  - CDER
  - CBER
  - NCTR
  - CFSAN

Examples of CDER Research in Nanotechnology

- Particle size determination in marketed sunscreens with TiO_2 and ZnO nanoparticles.
- Development of in vitro assays to assess toxicity of selected nanoparticles (collaboration with CDRH).
- Manufacture of nanoformulations and characterization of physical and chemical properties.

Examples of CDER Research in Nanotechnology (Cont'd)

- Evaluation of excipient effects on nanotechnology products.
- Evaluation of the effects of preparation methodology, process and formulation variables on nanotechnology product characteristics (including mathematical modeling of variables).
- Evaluate the stability and pre-clinical bioavailability of certain selected nanotechnology products.

Examples of CBER Research in Nanotechnology

- **FDA-NCI Clinical Proteomics Program**
  - **Interagency Agreement with NCI. Nanotechnology collaboration to evaluate and analyze clinical material from eventual NCI-based nanotechnology applications.**
- **Developing novel protein microarray based phosphoproteomic endpoint analysis of *in vivo* nanoparticle toxicity screening.**

Examples of CBER Research in Nanotechnology (Cont'd)

- Assessing nanoparticle ADME- animal imaging studies combined with laser capture microdissection.
- Developing nanoporous filtering devices for disease biomarker discovery.
- Developing and manufacturing nanoparticle biomarker "harvesting" agents- combined with mass spectrometry based profiling.

Examples of CFSAN Research in Nanotechnology for Cosmetics

Collaboration with NCTR/NTP/Rice U.:

- **Evaluating the effects of varying nano-size on the penetration of quantum dots through human and pig skin.**
- **Evaluating the penetration of TiO2 and ZnO nanoparticles through human skin.**
- **Evaluating the photocytotoxicity of TiO_2 nanoparticles using human skin fibroblasts.**

Examples of NCTR Research in Nanotechnology

- Evaluating the effect of size and coating on dermal penetration of quantum dots in skin of hairless mice (collaboration with NTP and Rice University)
- Evaluating the toxicology of nanoscale TiO_2 and ZnO: market survey (size and coating); dermal penetration *in vitro* & in mice and pigs; PK and toxicogenomics in mice; phototoxicity *in vitro* & mice; photocarcinogenicity in mice (collaboration with NTP, CFSAN and Rice University)

Two Most Frequently Asked Questions:

- Who (which Center) will review nanotechnology products?
- What will be the requirements for nanotechnology products?

Who Will Review Nanotechnology Applications?

- Office of Combination Products will coordinate the regulatory framework for nanotechnology products.
- An FDA Center will be designated with the primary responsibility for review.
- However, consultations from other Centers will be sought.

What are the Testing Requirements for Nanotechnology Products?

- As new toxicological risks that derive from nanomaterials are identified, new tests will be required.
- Industry and academia need to plan and conduct the research to identify potential risks and to develop adequate characterization methodologies.
- FDA can help in this process.

FDA Nanotechnology Website

- For links to individual Centers, published guidance documents and other relevant information on nanotechnology activities at FDA:
  - www.FDA.GOV/NANOTECHNOLOGY